REMARKS

Claims 1-3, 8-10, 18-20, and 27-30 are pending.

Claims 1-3, 8-10, 18-20, and 27-30 were all previously allowed (Office Action of 15 July 2004, and Office Communication dated 24 February 2005), however except for claims 27 and 28, which remain allowed, Claims 1-3, 8-10, 18-20, and 28-30 were rejected when a new Examiner took over the case when the prior Examiner left on maternity leave.

Applicants thank the Examiner for withdrawing the Examiner's prior rejections based on indefiniteness, alleged new matter with respect to the Sequence Listing, alleged lack of enablement for anti-HER-2 antibody containing formulations, and alleged anticipation in view of Scott et al.

Applicants thank the Examiner for initialing the p49 for two foreign patent references (WO0161356 and WO05016966) provided in applicants' IDS of 24 August 2005 that was considered by the Examiner on 27 October 2005.

Applicants acknowledge the Examiner's maintained rejection of claims 1-3, 8-9, 18-20 and 29-30, under 35 USC 112 first paragraph as allegedly lacking *enablement*. Applicants have respectfully *traversed* this rejection, and provide signed Affidavits by Dr. Gail Clinton in further support.

Applicants acknowledge the Examiner's *new grounds* of rejection of claims 8-10, 18, 29 and 30, under 35 USC 112 first paragraph as allegedly lacking *written description*. Applicants have respectfully *traversed* this rejection, and cite further support in the specification.

No new matter has been added.

FORMALITIES

Inconsistent Protracted Examination. Applicants respectfully maintain the objection to the present inconsistent, protracted, expensive, burdensome examination, and the non-responsiveness by the Office. Applicants' statements in this regard are of record in this case and are hereby reaffirmed and reasserted. Applicants note that Applicants' various applications covering this

subject matter are additionally now split between two different art groups with different Supervisory Examiners, and again respectfully request that the subject matter be consolidated in a single art group with the original Examiner Anne L. Holleran who is responsible for Applicants' other cases on this subject matter so that a more efficient consistent Examination can be conducted and finalized.

35 U.S.C. §112, first paragraph

Claims 1-2, 8-9, 18-20 and 29-30 are rejected, under 35 U.S.C. §112, first paragraph, as having an allegedly broad scope that is not commensurate with the specification. Specifically, it is alleged that while the specification is enabling for an isolated polypeptide *consisting of* SEQ ID NO:1 or comprising SEQ ID NO:2, it does not reasonably provide enablement for any polypeptide comprising SEQ ID NO:1, having from about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419 or about 350-419 amino acids from SEQ ID NO:2, which bind to the extracellular domain of HER-2.

In particular, the Examiner urges that the specification teaches that p68HER-2 and ECDIIIA bind to p185HER-2, but provides no evidence that any other isolated polypeptide would so function. The Examiner points to several references that allegedly teach how single amino acid substitutions can lead to dramatic changes in biological activity. The Examiner urges that although the specification teaches that the binding affinity resides in the 79 amino acid terminal portion of p68HER-2 (*i.e.* ECDIIIa), the residues critical for this binding have not been identified. Thus, the Examiner urges that one could not predict which truncated version of the 79 amino acid portion would retain its ability to bind HER-2. Further, the Examiner prophetically argues that the claimed subject matter encompasses polypeptides that would be expected to have an altered configuration, folding or shape (*i.e.* due to truncations or additions), and that one could not predict whether such an alteration of the polypeptide would function as claimed.

Because of this, the Examiner urges that Applicants' claims reciting subfragments of the 79 amino acid ECDIIIa region should be view as 'screening assay' claims, and in mantra-like fashion, the Examiner repeatedly cites, albeit inappropriately, *Rochester v. Searle*, 358 F.3d 916, Fed. Cir.,

2004 for the proposition that 'screening assays, instantly suggested Applicant, are not sufficient to enable an invention because they are merely a wish or a plan for obtaining the claimed chemical invention.

The Examiner concludes that in the absence of any guidance or working examples, the specification provides no evidence that one of skill in the art could predict that the subject matter functions as claimed without undue experimentation.

This rejection is respectfully *traversed* in the arguments presented here below, because the enablement requirement is in fact met under U.S. patent law, because the Examiner has grossly misconstrued *Rochester v. Searle* in two fundamental respects, and because there is reasonable scientific basis to support the original conception as claimed.

Relevant Law:

Applicants maintain that to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without *undue* experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of §112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." In re Marzocci et al., 469 USPQ 367 (CCPA 1971) (emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred

embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

There is, therefore, no requirement for disclosure of every species within a genus. Applicants are entitled to claims that are commensurate in scope not only with what applicants have specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicants have disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require ***undue*** experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, with include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Formann, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Wands Analysis:

Applicants reaffirm and reassert Applicants' arguments of record. As described below, a consideration of the factors enumerated in In re Wands demonstrates that the application, in conjunction with what was known to one of skill in the art as well as the other relevant factors, teaches how to make and use the full scope of the claimed subject matter. General techniques for isolating, expressing, and testing polypeptides comprising all or part of the sequence of p68HER-2 set forth in SEQ ID NO:2, including the ECDIIIa portion set forth in SEQ ID NO:1, are provided in the specification and are known to the skilled artisan, as discussed in detail below, and any necessary adjustment can be determined empirically using routine testing. Having taught the full length polypeptide and the ECDIIIa portion and demonstrated binding thereof, and having taught assays for testing polypeptides that contain portions of these polypeptides to assess activity, it would not require undue experimentation to identify polypeptides that bind to the ECD of HER-2 with an

affinity binding constant of at least 10^8M^{-1}. It would, therefore, not require undue experimentation for one of skill in the art to make and use the claimed subject matter. This is particularly true in view of the guidance provide by the recitation of 50-79 contiguous amino acids, as can be appreciated in view of the presently attached Affidavits of Dr. Gail Clinton, which will be discussed after the following *Wands* analysis:

1) ***Scope of the Claims***. The claims are directed to isolated polypeptides of p68HER-2, or fragments thereof including the 79 amino acid terminal fragment of p68HER-2 termed ECDIIIa, that bind to the ECD of HER-2 with a specified binding affinity, and to pharmaceutical compositions that contain the polypeptides. Claim 1 is directed to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1, or fragments thereof that are about 50 to 79 contiguous residues in length that binds to the ECD of HER-2. Dependent claim 2 specifies that the polypeptide is from about 69 to 79 amino acids in length. Claim 8 is directed to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2, or fragments thereof that are about 80 to 419 amino acids in length that contain the 79 amino acid C-terminal portions and that bind to the ECD of HER-2. Dependent claim 9 specifies that the polypeptide is from about 350 to 419 amino acids in length and contains three N-linked glycosylation sites. Claims 18-20 and 29-30 are directed to pharmaceutical compositions containing the polypeptides set forth in claims 1-2 and 8-9, respectively.

The claims are clearly within the scope of what is taught in the specification, *i.e.*, a genus of polypeptides of p68HER-2 that includes the particular claimed polypeptides. The specification teaches that p68HER-2 binds to the ECD of HER-2, and further teaches that a fragment thereof of 79 amino acids also binds to the ECD of HER-2. The specification teaches the sequence, expression, cloning, and purification of p68HER-2 and related truncated polypeptides (*i.e.* the 79 amino acid ECDIIIa peptide), and provides detailed assays for assessing their binding affinity. These same assays, as readily recognized by one of skill in the art, also provide detailed assays for assessing binding affinity or subfragments of p68HER-2 and ECDIIIa. By following the teachings of the specification, one of skill in the art can readily make the claimed polypeptides and measure their

binding affinity. Therefore, the scope of the claims is commensurate with the teachings of the specification.

2) ***Level of Skill in the Art.*** The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

3) ***Knowledge of those of Skill in the Art.*** At the time of filing of the instant application, a broad body of knowledge was available and known about HER-2 and other tyrosine kinases. Many of these articles and patents have been made of record in this application. For example, the sequence of HER-2 was known, its structural and biochemical properties determined, and its overexpression associated with a variety of carcinomas. Truncated variants containing regions of the extracellular domain (ECD) of a variety of HER family RTKs was known, many of them produced by proteolytic processing of full length receptors or by alternative processing (see *e.g.*, Lee and Maihle, (1998) Oncogene, 16:3243). For example, truncated variants of HER-2 were known and analyzed for function. Among these include a proteolytically shed product containing the extracellular domain (ECD) found in breast carcinomas, and a truncated ECD of HER-2 generated as an alternative transcript (see *e.g.*, Scott et al., (1993) Mol. Cell. Biol. 13:2247). In addition, a truncated ECD of related EGFR also was known, and characterized to exhibit ligand-binding, and affect the function of receptor activation and signaling (see *e.g.*, Basu *et al.*, (1989) *Mol. Cell. Biol.*, 9:671).

The above references exemplify a variety of published protocols for the identification, production and/or analysis of truncated receptor tyrosine kinase products, including truncated HER-2 polypeptides, and the analysis of such peptides in binding assays and/or or other functional assays. The references show that such procedures were available at the time of filing of the application, and thus evidence the state of the art at the relevant time.

4) ***Teachings of the Specification and Working Examples.*** As discussed herein, the claims are directed to p68HER-2 polypeptides and fragments thereof that bind to the ECD of HER-2 with a binding affinity of $10^8 M^{-1}$. Included among these polypeptides are polypeptides or fragments

of polypeptides having the sequence of amino acids set forth in SEQ ID NO:1 or SEQ ID NO:2. Hence, the "genus" encompasses the exemplified species and other species that are similar to the exemplified species because they exhibit all or part of the sequence of SEQ ID NO:1 or SEQ ID NO:2 and have binding affinity for the ECD of HER-2. The specification teaches such genus of polypeptides and teaches their sequence, cloning, expression, and purification and assays to test their binding affinity to the ECD of HER-2.

The specification teaches the detailed structural and functional characterization of a naturally occurring inhibitor of HER-2, p68HER-2. The specification describes that p68HER-2 binds to p185HER-2 and that the binding affinity of p68HER-2 resides in the novel proline rich ECDIIIa domain, rather than the N-terminal subdomains I and II of p68HER-2. The specification teaches that the proline rich ECDIIIa domain is a retained intron 8 sequence of 79 amino acids. The specification teaches how to clone, purify, and test the binding affinity of the 79 amino acid fragment of p68HER-2. The specification, and declarations of record, also teach exemplary anti-tumor assays.

The Working Examples exemplify the teachings of the specification. Because these have already been summarized in Applicant's last Response, they will not be reproduced here. Nonetheless, as demonstrated, the specification provides detailed knowledge and Working Examples of the characterization, cloning, purification, and function of p68HER-2, and polypeptide fragments thereof (*i.e.* 79 amino acid fragment).

5) ***Predictability.*** As is known to those of skill in the art (described above), the level of knowledge and skill in the identification, characterization, cloning, purification, and testing of alternative HER isoforms, including the p68HER-2 polypeptide and fragments thereof as claimed in the instant application, was high as of the effective filing date. Therefore, given the extensive teachings of the specification, in combination with what was known at the time the instant application was filed, it is not unpredictable that p68HER-2 and fragments thereof can be generated and tested for their ability to bind p185HER-2, and those that bind identified.

The Office Action alleges that the specification provides insufficient guidance with regard to making the broadly claimed polypeptides and that one of skill in the art would be unable to predict

the claimed subject matter would function with a reasonable expectation of success. Specifically, the Examiner urges that in the absence of knowing the residues of ECDIIIa that are critical to binding, it could not be predicted which truncated version of SEQ ID NO:1 would function. In addition, the Examiner urges that the effects of truncations of SEQ ID NO:1 or SEQ ID NO:2 cannot be predicted because the truncations would be expected to alter the configuration of the polypeptide which would be expected to affect the conformation of the binding site. Similarly, the Examiner urges that a polypeptide *comprising* SEQ ID NO:1 would include unlimited amino acid residues at one or both of the N or C terminus, which also would alter the protein folding and could "mask" the sequence of SEQ ID NO:1 required for binding. In support of this, the Examiner cites a number of references that teach how single amino acid substitutions can lead to dramatic changes in biological activity (*i.e.*, Bowie *et al.*; Rudikoff *et al.*; Burgess *et al.*).

It is respectfully submitted that each of the above reasons is not relevant to the issue under consideration. The claims are directed to polypeptides of SEQ ID NO:1 or SEQ ID NO:2, or fragments thereof, that ***bind to p185HER-2 with a binding affinity of $10^8 M^{-1}$***. This functional limitation naturally excludes polypeptides that would not bind to p185HER-2 because, for example, they no longer contain the binding site and/or the polypeptides are folded in such a way to "mask" the binding site.

Furthermore the specification teaches the entire sequence of the polypeptides, demonstrates activity of several and provides assays to assess the activity of any others. Systematically removing residues and, if necessary, testing the resulting polypeptides for activity is routine and readily achieved. The sequence of every such polypeptide is known in view of the disclosure of the application.

Given that the specification teaches that a polypeptide of SEQ ID NO:2 of 419 amino acids, *and* a polypeptide fragment thereof of 79 amino acids set forth in SEQ ID NO:1, bind to p185HER-2, it is not unpredictable that other polypeptide fragments also bind p185HER-2. Importantly, the specification teaches that a polypeptide *comprising* SEQ ID NO:1 (*i.e.* a his-tagged ECDIIIa peptide, or p68HER-2) binds to p185HER-2. One of skill in the art could predictably make the polypeptides as claimed, such as by using standard recombinant DNA techniques to serially truncate

the sequence of SEQ ID NO:1 and SEQ ID NO:2, and test the resulting polypeptides for their ability to bind p185HER-2.

Yet, the Examiner urges that the present specification does not reasonably provide enablement for any "polypeptide comprising SEQ ID NO:1, having from about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419 or about 350-419 amino acids from SEQ ID NO:2, which bind to the extracellular domain of HER-2." The Examiner is respectfully requested to further reconsider this rejection based on the following additional comments.

First, the claims to refer to *contiguous* residues (e.g. to "50-79 contiguous" or "69-79 contiguous" residues), which reasonable should alleviate much of the Examiner's concern.

Second, the instant teachings and examples show that p68HER-2, and the intron-encoded ECDIIIa subregion thereof, both bind with a very high affinity to HER-2. Significantly, the fact that high affinity binding is retained by the 79 amino acid ECDIIIa subregion would not suggest to one skilled in the art that the entire 79 amino acids are *essential* for high-affinity binding, but rather only that the minimal region sufficient for binding is contained therein. Accordingly, applicants have justifiably claimed a somewhat smaller *contiguous* region, limited, by the recited functional proviso that the region must still demonstrate high-affinity binding (at least 10^8 M^{-1}) to HER-2, the hallmark of the present invention. Thus applicants teach a region, and further teach how to rapidly identify operative embodiments. The functional binding limitation serves to assure that the scope of the claimed subject matter is commensurate with the teachings of the specification. The scope of the claimed genus is substantially narrowed by recitation of contiguous amino acid residues.

Third, in further confirmation of the reasonable basis for claiming regions of at least 50 contiguous amino acids, several of applicants' copending applications disclose specific active polymorphic variants of Herstatin that correspond to *non-conservative* amino acid substitutions. Significantly, 6 of these non-conservative variable positions occur within the first 21 amino acid positions. This finding confirms the instant teachings and disclosure that the minimal binding region is contained in a subregion of ECDIIIA (*e.g.*, of about 50 to 79 residues).

Fourth, the instant specification teaches heterologous fusion proteins with the ECDIIIa region. Applicants have demonstrated and taught the binding properties of the full-length p68HER-

2 and the ECDIIIa sub-fragment (*see* Example 9, and Figure 5). The particular ECDIIIa sub-fragment tested in Example 9 was expressed from the pET30a vector (Novagen; see specification at page 17, line 11-12) and thus represents a significant *fusion* protein of ECDIIIa (referred to herein as the His-tagged ECDIIIa fragment (ECDIIIa fragment)), comprising a heterologous amino terminal region of about 50 amino acids having: a poly-histidine tag; a thrombin cleavage site; an S-tag region; and an enterokinase site. Therefore, applicants have not only disclosed a smaller contiguous binding region, but have demonstrated its function in the context of much larger polypeptides; namely p68HER-2, and more significantly—a sizable *diverse* fusion protein. Therefore, contrary to the position urged by the Examiner, a person of ordinary skill in the art would not reasonably conclude that added amino acids would obscure and prevent SEQ ID NO:1 residues from mediating high-affinity binding to p185HER-2.

Fifth, Applicants herein submit an Affidavit by inventor Dr. Gail Clinton, which addresses the Examiner's concern that in the absence of knowing the residues of ECDIIIa that are critical to binding, it could not be predicted which truncated versions would function because the truncations would be expected to alter the configuration of the polypeptide which would be expected to affect the conformation of the binding site. In fact, as is apparent from the affidavit, Applicants did know, based on a hydrophobicity analysis, what residues would be expected to be important for folding and binding activity, and this knowledge provided the conceptual support for, and was memorialized in the claimed recitation of "50-79 contiguous amino acid residues of SEQ ID NO:1." Specifically, the unique 79 amino acid sequence of the ECDIIIa (intron-encoded) domain of Herstatin was analyzed as a standard Kyte Doolittle hydropathy plot (Clinton Affidavit, Figure 1; attached hereto). This data/figure (obtained in 1998) shows that the first 32 residues of the ECDIIIa sequence are hydrophilic, 16 residues (amino acids 32-48) constitute a central hydrophobic domain, and the C-terminal 30 amino acids of ECDIIIa are hydrophilic. This data identified a hydrophobic ECDIIIa subdomain that Applicants regarded as critical not only for Herstatin and ECDIIIa domain binding activity, but also for protein folding and binding activity of ECDIIIa subdomains that comprised this central hydrophobic subdomain. Therefore, the basis of explicitly claiming subfragments of 50-79 contiguous amino acids followed from the central position of the

hydrophobic residues amino acids 32-48 with the 79 aa ECDIIIa region, and the fact that such hydrophobic regions were widely recognized in the art to be generally critical for protein folding and for protein-protein interactions (*e.g.,* for folding, and for receptor binding). Essentially, therefore, this aspect of the conception was that the smallest contiguous fragment that yet included the hydrophobic domain would reasonably be able to fold properly and bind. It was appreciated by Applicants at the time that any contiguous stretch of 50 amino acids, regardless of where such stretch is located within the ECDIIIa sequence, will include the central hydrophobic domain.

Therefore, ECDIIIa subfragments of 50-79 amino acids having high-affinity binding activity were encompassed and articulated as part of Applicants' original conception, and were thus explicitly claimed in the originally-filed specification and claims. Additionally, the validity and basis of this aspect of the conception has been further confirmed by the fact that non-conservative ECDIIIA polymorphic variants outside the hydrophobic region, as described in an earlier Affidavit (attached hereto) that was filed on 28 January 2005 in Applicant's U.S. Patent Application Serial No. 09/506,079, did not abrogate high-affinity binding to p185HER-2. The hydrophobicity analysis not only provided a substantially reasonable scientific basis, for claiming proteins that comprise 50-79 contiguous amino acids of the ECDIIIa domain and that bind with high affinity to p185HER-2, but also supports Applicants' position that the invention as originally conceived and claimed can be practiced without 'undue' experimentation, because of guidance provided by the knowledge of the positioning of the hydrophobic region as memorialized by the recitation of "50-79 contiguous amino acid residues..."—as reflected in Applicants' originally filed claims and specification.

Thus, the teachings of the specification are widely applicable to make and use truncated fragments of SEQ ID NO:1 or SEQ ID NO:2 that exhibit binding affinity to p185HER-2. The specification provides detailed procedures and assays to generate the polypeptides and to test the binding affinity of truncated polypeptides. Therefore, it is respectfully submitted that a high degree of knowledge was available at the time of filing of the instant application, to render the instantly claimed polypeptides predictably generated and tested for binding affinity to p185HER-2.

Conclusion. In light of the scope of the claims, the teachings in the specification, the presence of specific working examples in the specification, the high level of skill of those in this art,

the knowledge of those of skill in this art, and the predictability of the subject matter, it would not require undue experimentation for a person of skill in the art to isolate a p68HER-2 polypeptide, or fragment thereof, and determine its binding affinity to the ECD of p185HER-2. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter.

Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rebuttal to Examiner's Arguments:

In addition, it is respectfully submitted that analysis of enablement requires consideration of all of the "Wands Factors;" focusing on one or two is a misapplication of the law. All factors must be considered and weighed. A deficiency in meeting one factor does not preclude a finding of enablement. In the instant case, the Examiner only urges that it is not predictable what effects truncations or addition of SEQ ID NO:1 or SEQ ID NO:2 would have on the function of the polypeptides. It is noted that predictability is only one factor that should be considered. The claimed subject matter requires that the polypeptides bind to the ECD of p185HER-2 with a specified binding affinity. Given the teachings of the specification, presence of working examples, the state of the prior art, and the relative skill of the in the art, one of ordinary skill in the art could predictably generate polypeptides as claimed.

Further, the reliance on *Rochester v. Searle* (*358 F.3d 916, Fed Dir., 2004*) is misplaced; it addresses written description not enablement, which are distinct. In addition, the facts pertinent to the findings in *Rochester v. Searle* are distinct from the instant claims. The claims at issue in the Rochester '850 patent were directed to ***screening assays*** for use in determining whether a particular drug selectively inhibited the activity of COX-2, which was thought to be responsible for the inflammation associated with diseases such as arthritis, without inhibiting COX-1 activity. The '850 patent did not disclose ***any*** compound that would function as claimed, nor provided any suggestion as to how such a compound could be made or otherwise obtained other than by trial-and-error research. Thus, the court concluded that the '850 patent lacked adequate written description; the question of enablement was considered moot and not addressed in the Federal Circuit decision.

Specifically, in *Univ. of Rochester v. G.D. Searle & Co.*, the Federal Circuit affirmed a grant of summary judgment that the patent at issue was invalid for "failing to comply with the written description requirement of 35 U.S.C. § 112 ¶1." *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 69 U.S.P.Q.2d 1886 (Fed. Cir. 2004). Because the Federal Circuit affirmed the district court's decision on the written description ground, it "consider[ed] the enablement issue to be moot." Id. at 69 U.S.P.Q.2d 1897.

While the Federal Circuit did not address whether the invention was enabled, the court upheld previous decisions holding the written description requirement is independent from the enablement requirement and one of these requirements may be satisfied even though the other is not. Id. at 69 U.S.P.Q.2d 1891. Consequently, while some overlap exists between the requirements, the analysis is different for each:

> Thus, an invention may be described without an enabling disclosure of how to make and use it. A description of a chemical compound without a description of how to make and use it, unless within the skill of one of ordinary skill in the art, is an example. Moreover, an invention may be enabled even though it has not been described. Such can occur when enablement of a closely related invention A that is both described and enabled would similarly enable an invention B if B were described. A specification can likewise describe an invention without enabling the practice of the full breadth of its claims.

Id. at 69 U.S.P.Q.2d 1891 (citations omitted).

In *Rochester*, all of the claims at issue were directed toward "A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product ...." Id. at 69 U.S.P.Q.2d 1888. The "patent neither disclose[d] any such compound nor provide[d] any suggestion as to how such a compound could be made or otherwise obtained other than by trial-and-error research." Id., 69 U.S.P.Q.2d at 1889 (citing Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp. 2d 216, 224-25, 228-29, 68 U.S.P.Q.2d 1424 (W.D.N.Y. 2003)) "[T]he [trial] court found no evidence in the '850 patent that the inventors themselves knew of any such compound at the time their patent application was filed." Id. Further, the Federal Circuit found "[e]ven with the three-dimensional structures of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them, let alone have been within the

purview of one of ordinary skill in the art in the 1993-1995 period in which the applications that led to the '850 patent were filed" and the patent owners experts did not offer any persuasive evidence to the contrary:

> Tellingly, ... what plaintiff's experts' [sic] do not say is that one of skill in the art would, from reading the patent, understand what compound or compounds—which, as the patent makes clear, are necessary to practice the claimed method—would be suitable, nor would one know how to find such a compound except through trial and error .... Plaintiff's experts opine that a person of ordinary skill in the art would understand from reading the '850 patent what method is claimed, but it is clear from reading the patent that one critical aspect of the method—a compound that selectively inhibits PGHS-2 activity—was hypothetical, for it is clear that the inventors had neither possession nor knowledge of such a compound.

Id. at 69 U.S.P.Q.2d 1894 (citing 249 F. Supp. 2d at 229).

In affirming the district courts decision, the Federal Circuit summarized its reasoning as follows:

> In sum, because the '850 patent does not provide any guidance that would steer the skilled practitioner toward compounds that can be used to carry out the claimed methods—an essential element of every claim of that patent—and has not provided evidence that any such compounds were otherwise within the knowledge of a person of ordinary skill in the art at the relevant time, Rochester has failed to raise any question of material fact whether the named inventors disclosed the claimed invention. Accordingly, we affirm the district court's grant of Pfizer's motion for summary judgment.

Id. at 69 U.S.P.Q.2d 1897.

In contrast, the instant claims are *not directed to screening assays*, but are directed to the polypeptides, which are disclosed in the application. The application provides polypeptides, including their sequence, cloning, purification, and methods for testing their binding to p185HER-2. Applicants' "genus" encompasses the exemplified species and other species that are similar to the exemplified species because they exhibit all or part of the sequence of SEQ ID NO:1 or SEQ ID NO:2 and have binding affinity for the ECD of HER-2. Furthermore, the specification teaches the entire sequence of the polypeptides, demonstrates activity of several and provides assays to assess the activity of any others. Systematically removing residues and, if necessary, testing the resulting polypeptides for activity is routine and readily achieved. The sequence of every such polypeptide is known in view of the disclosure of the application. Furthermore, as is apparent from the attached Affidavit of Dr. Gail Clinton, the recitation of "50-79 contiguous amino acid residues..." did not only serve to memorialize the knowledge gained from the location of the central hydrophobicity

region, but also serves as a scientifically-based 'road-map' for the construction of active truncated fragments. Thus, the findings in *Rochester v Searle* are not on point, and are inapt with respect to the instantly claimed subject matter, and even if apt, do not lead to a conclusion of lack of enablement, since the instant application provides compounds that have the requisite activity. Moreover, even if considered from the standpoint of *written-description*, the Affidavit of Dr. Gail Clinton confirms that there was a reasonable scientific basis for the originally recited fragments, based on the central position of the hydrophobic region as described herein and in Dr. Clinton's Affidavit.

Public policy considerations. Applicants are entitled to claims that are commensurate in scope not only with what applicants have specifically described and exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicants have disclosed. In this instance, applicants invention is pioneering in several senses, including in the sense that for the first time ever Applicants identified a ligand for HER-2, which at the time was essentially an orphan receptor that was implicated in many types of cancer, and there was a pronounced need in the art for HER-2 antagonists. Applicants have disclosed and taught several variants of p68HER-2, including a truncated form that contains only the intron-encoded portion (*i.e.* ECDIIIa). Applicants are the first to identify any p68HER-2 (herstatin) polypeptide, and fragments thereof, and the first to recognize that the retained intron encoded portion (ECDIIIa) alone is able to bind to the ECD of p185HER-2.

It is unfair and unduly limiting and contrary to the public policy upon which the patents laws are based to require applicants to limit the claims to the exact sequences exemplified, when the application clearly teaches how to make and use polypeptides that vary from the exemplified polypeptides. See, for example, *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts."

The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the disclosure. This requires as much the granting of broad claims on

broad inventions as it does the granting of more specific claims on more specific inventions. *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

If applicants are required to limit the claims as suggested by the Examiner, then those of skill in the art can, by virtue of the teachings of this application, readily prepare polypeptides that differ in a few residues, thereby practicing what is disclosed in the application, but avoiding infringing such limited claims. The instant application provides a broader disclosure; and having done so, places the public in possession of such knowledge. Having provided this disclosure, it permits others to benefit therefrom. Those of skill in the art should not be permitted to practice what is taught in the application, but avoid infringing the claims. To permit that is simply not fair. Small early stage companies can ill-afford to dedicate their innovations to the public.

Additional Rejection under 35 U.S.C. §112, first paragraph

Claims 18-20 and 29-30 remain rejected, under 35 U.S.C. §112, first paragraph, as allegedly being broader than the enabling disclosure. Specifically, it is alleged that while the specification is enabling for a pharmaceutical composition for treating solid tumors that overexpress HER-2, where the composition comprises a polypeptide of SEQ ID NO:2, the specification does not reasonably provide enablement for any pharmaceutical composition containing a polypeptide whose sequence consists of SEQ ID NO:1, comprises SEQ ID NO:1, or comprises the claimed fragments of SEQ ID NO:1 or SEQ ID NO:2.

In particular, the Examiner urges that although the specification and Declarations of record exemplify the efficacy of p68HER-2 (set forth in SEQ ID NO:2), it cannot be predicted that any other isolated polypeptide would function as claimed. The Examiner concludes that in the absence of any guidance or working examples, the specification provides no evidence that one of skill in the art could predict that the subject matter functions as claimed without undue experimentation. This rejection respectfully is traversed.

For the reasons detailed above, it is respectfully submitted that the teachings in the specification, the presence of specific working examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in this art, and the predictability of the subject

matter, it would not require undue experimentation for a person of skill in the art to make and use a pharmaceutical composition as claimed for treating solid tumors that overexpress HER-2. Insofar as p68HER-2, and polypeptide fragments thereof, are enabled, pharmaceutical compositions containing these polypeptides also are enabled.

Specifically, the specification provides explicit teaching of anti-tumor cell activity by p68HER-2 in an assay assessing anchorage independent growth of cells in soft agar, which is an art recognized and predictive procedure to examine transforming activity (see *e.g.*, page 13, lines 5-23, and Figure 7). Specifically, the specification teaches that p68HER-2 inhibits anchorage independent growth of two cells lines (SKOV-3 and 17-3-1 cells, both which overexpress HER-2). In addition, the Declarations of record of November 22, 2002 by Dr. Gail Clinton and Dr. Edward Neuwelt further demonstrate the efficacy of p68HER-2 in *in vivo* models of tumor cell activity using other art recognized assays that were known to one of skill in the art at the time of filing the instant application.

Importantly, the Declarations, and references of record therein, evidence the high level of skill in the art and knowledge of skill in the art, particularly with respect to assaying for compounds for treating solid tumors. Thus, it is respectfully submitted that a high degree of knowledge was available at the time of filing of the instant application, that in combination with the teachings of the specification, render the instantly claimed compositions predictably generated and tested for anti-tumor activity. Furthermore, as is apparent from the attached Affidavit of Dr. Gail Clinton, the recitation of "50-79 contiguous amino acid residues..." did not only serve to memorialize the knowledge gained from the location of the central hydrophobicity region, but also serves as a scientifically-based 'road-map' for the construction of active truncated fragments.

Furthermore, the Examiner has provided no evidence that the polypeptides cannot be formulated as a pharmaceutical compositions and so-used. The claims recite that the polypeptides have a recited binding affinity, which the exemplified polypeptides possess. The Examiner has provided no evidence that a polypeptide that has such affinity does not possess pharmaceutical activity.

Applicants, therefore, respectfully request withdrawal of this rejection.

Further Rejection under 35 U.S.C. §112, first paragraph

Claims 8-10, 18, 29 and 30 are rejected on new grounds, under 35 U.S.C. §112, first paragraph, as allegedly lacking *written description.*

Specifically, the Examiner alleges that there is no support for recitation of 'an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2, or a fragment thereof wherein the polypeptide binds to the extracellular domain of HER-2 with an affinity binding constant of at least 10^8 M^{-1}'.

This rejection is respectfully traversed.

Applicants original specification describes a *genus* of compounds that comprises SEQ ID NO:1, or 50-79 contiguous amino acid-containing fragments thereof, and that bind at nanomolar concentrations, meaning that they would have a binding affinity "of at least 10^8" as recited. Applicants point out that SEQ ID NOS: 1 and 2 are related, in that SEQ ID NO:1 is comprised withing SEQ ID NO:2. Clearly, because SEQ IN NO:2 or any polypeptide comprising SEQ ID NO:2, or that comprises the C-terminal contiguous 79 amino acid residues thereof, would also comprise SEQ ID NO:1 and would thus be encompassed by a *genus* of compounds that comprises SEQ ID NO:1, or 50-79 contiguous amino acid-containing fragments thereof, and that bind at nanomolar concentrations (i.e., affinity of at least 10^8).

Moreover, it is clear from the specification that Applicants considered that p68HER-2 bound at least as well, if not better than the ECDIIIa subportion thereof. The specification at page 7 for example, in the legend to Figure 7, describes the use of nanomolar concentrations of p68HER-2 for binding to SKOV-3 cells. Additionally, the specification at page 8, recites that "the unique ECDIIIa peptide binds with high affinity (nM concentrations) to p185HER-2 and to transfected 17-3-1 cells that overexpress p185HER-2 (Figure 5)," and further states that "[t]herefore, p68HER-2 and fragments thereof appear to be a naturally occurring HER-2 binding protein, encoded by the HER-2 gene." Therefore, the SEQ ID NO:1 containing fragments are disclosed as binding with an affinity of at least 10^8 and are referred to as high affinity binders that can be used a nanmolar concentration. The specification clearly teaches that p68HER-2 (SEQ ID NO:2) is also regarded as binding with an

affinity of at least 10^8, because it is used at nanomolar concertrations in the specification Examples, and as described above, SEQ IN NO:2 or any polypeptide comprising SEQ ID NO:2, or that comprises the C-terminal contiguous 79 amino acid residues thereof, would also comprise SEQ ID NO:1 and would thus be encompassed within, and thus defined by a *genus* of compounds that comprises SEQ ID NO:1, or 50-79 contiguous amino acid-containing fragments thereof, and that binds at nanomolar concentrations (i.e., affinity of at least 10^8).

Applicants, therefore, respectfully request withdrawal of this rejection.

Claims 8-10 and 18 are rejected on new grounds, under 35 U.S.C. §112, first paragraph, as allegedly lacking *written description.*

Specifically, the Examiner stated that the basis of her rejection for these claims was that the recitation concerning the number of glycosylation sites introduced new matter into the specification (item 7, page 12 Office Action). The Examiner cites claims 8-10 and 18 for lacking written description because they are drawn to polypeptides comprising "at least one N-linked glycosylation site" and the Examiner alleges that there is no support in the specification for the limitation of "at least one N-linked glycosylation site." Additionally, the Examiner has also called out claim 9 for including the limitation of "at least three N-linked glycosylation sites."

Applicant respectfully traverses this rejection, based on the fact that there is explicit literal support for this limitation on page 5, line 23, and page 16 line 5, where the specification describes "a consensus asparagine linked glycosylation site." As recognized in the art, and including to one of ordinary skill in the art, "N-linked" and "asparagine linked" refer to the same amino acid, because "N" is the single letter abbreviation for asparagine. The specification thus teaches a single asparagine linked site at page 5, line 23, and page 16 line 5, and there is consequently support in the specification for the limitation of "at least one N-linked glycosylation site" recited in claims 8-10 and 18. Likewise, we agree with the Examiner (item 9, page 13 of the Office Action) that there is disclosure in the specification for "at least three N-linked glycosylation sites." Furthermore, the specification discloses that subdomains I and II of the ECD portion of herstatin contain five N-glycosylation sites and that the novel 79 aa portion contains one consensus N-linked glycosylation

site. Thus, a polypeptide of 80-419 amino acids that contains the 79 amino acid portion has "at least one" N-linked glycosylation site present, and depending on the length of the polypeptide, other N-linked glycosylation sites can also be present.

Applicant, therefore, respectfully requests withdrawal of the Examiner's new matter rejection based on an alleged lack of written description for the number of glycosylation sites, where there is explicit literal support in the originally filed specification as cited herein, and as appreciated by the Examiner.

Claims 18 and 30 are rejected on new grounds, under 35 U.S.C. §112, first paragraph, as allegedly lacking *written description.*

Specifically, the Examiner stated there is no support for recitation of "combinations thereof, with the proviso that where the composition comprises the monoclonal antibody it also comprises at least one of the agents of (a) and (b)."

Applicant respectfully traverses this rejection, based on the fact that there is explicit literal support for this limitation on page 9, line 31 through page 10 line 9, where the specification describes

> The present invention further provides a pharmaceutical composition for treating solid tumors that overexpress HER-2, comprising an agent selected from the group consisting of (a) an isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8, (b) an isolated and glycosylated polypeptide having from about 300 to 419 amino acids taken from the sequence of SEQ ID NO. 2, wherein the C terminal 79 amino acids are present, and wherein at least three N-linked glycosylation sites are present, (c) a monoclonal antibody that binds to the ECD of HER-2, and (d) **combinations <u>thereof</u>**, with the proviso that the agent cannot be the monoclonal antibody alone, and pharmaceutically acceptable carrier. Preferably, the agent is the isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1. Most preferably, the agent is a combination of the isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1 and the monoclonal antibody that binds to the ECD of HER-2.

Specification page 9, line 31 through page 10 line 9 (emphasis added).

Applicants explicit recitation of "combinations thereof", by virtue of reciting "thereof", does not as urged by a previous Examiner (Office action of 21 October 2003) allow the proviso ("that the agent cannot be the monoclonal antibody alone") to be interpreted as allowing the antibody to be in combination with "any second agent". This is because "combination thereof" must be combinations thereof (i.e., of (a) (b) and (c), and not combination of (c) with "any second agent" that is not (a) or (b). Furthermore, the combined phrases "combinations thereof" and "that the agent cannot be the monoclonal antibody alone" necessitates that the antibody must be present with at least one of agents (a) and agent (b).

Currently, claim 18 recites "that where the composition comprises the monoclonal antibody it also comprises at least one of the agents of (a) and (b)," and is this fully supported by the originally filed specification.

Applicant, therefore, respectfully requests withdrawal of the Examiner's new matter rejection.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request entry of the present Response and Amendment, and a Notice of Allowance relating to all pending claims, all having been previously allowed.

The Examiner is encouraged to phone applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite issuance of a final Notice of Allowance.

Respectfully submitted,

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